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Original Article

Maternal hyperhomocysteinemia and congenital heart defects: A prospective case control study in Indian population

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ABSTRACT

Objective: Very few studies have been conducted in this part of world to see relation between maternal serum homocysteine levels and congenital heart disease in their offsprings. With this perspective in mind, this study was carried out.
Methods: Fifty women were enrolled in this study. Thirty of these had delivered neonates who were diagnosed to have congenital heart diseases. These were treated as cases. Twenty of these women had delivered neonates who did not have any congenital heart diseases and were treated as controls. For estimating the levels of plasma homocysteine, fasting blood samples were taken from the women in both groups.
Results: Out of 30 cases, 14 (46.6%) had a tHcy level more than 15 μmol/l and all these women had delivered babies who were found to have congenital heart diseases. Out of controls, only 3 (15%) had a tHcy level more than 15 μmol/l. In babies with ventricular septal defects, the mean maternal plasma tHcy level was 13.30 μmol/l. In babies with Tetralogy of Fallot, the mean maternal plasma tHcy level was 40.07 μmol/l. In babies with Transposition of Great Vessels, the mean maternal plasma tHcy level was 40.93 μmol/l. In babies with Tricuspid atresia, the mean maternal plasma tHcy level was 24.89 μmol/l.
Conclusions: Increased levels of maternal serum homocysteine are associated with increased risk of occurrence of congenital heart defects in their offsprings, suggesting that maternal hyperhomocysteinemia is an independent risk factor for congenital heart defects.

1. Introduction

Congenital heart diseases are mainly the result of incomplete development of heart during the first six weeks of pregnancy. Although in recent years, several medical and surgical advances have improved the survival rates of infants with congenital heart diseases,[1–3] not all affected infants can be successfully treated surgically, and the treatment itself has considerable social, economic and personal costs.[3] Moreover, the long term prognosis of infants who have been surgically treated has not been clearly determined.[4] These concerns highlight the importance and potential impact of primary prevention of congenital heart defects. Studies in the recent past have shown that increased levels of maternal serum homocysteine are associated with increased risk of occurrence of congenital heart defects in their offsprings, suggesting that maternal hyperhomocysteinemia is an independent risk factor for congenital heart defects,[5–8] by interfering with the development of conotruncal septum of heart.

Very few studies have been conducted in this part of the world to see relation between maternal serum homocysteine levels and congenital heart disease in their offsprings. With this perspective in mind, this study was carried out.

2. Methods

This prospective study was carried out in a tertiary care hospital in north India over a period of one year. The study cohort was selected from the obstetric department of the hospital. Fifty women were enrolled in this study. Thirty of these had delivered neonates who were diagnosed to have congenital heart diseases (except patent ductus arteriosus, atrial septal defects and syndromal associations). These 30 women were treated as cases. Twenty of these women had delivered neonates who did not have any congenital heart diseases. These 20 women were treated as

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controls. In all these 50 women, there was no history of consumption of any multivitamin preparation in three months preceding delivery. Women from rural as well as urban backgrounds were included in the study.

The criteria for diagnosis of congenital heart diseases in neonates born to these women was based on detailed history and a thorough clinical examination, and confirmed by chest radiography, electrocardiography and echocardiography.

For estimating the levels of plasma homocysteine, fasting blood samples were taken from the women in both groups nine to fifteen months after the index delivery. The blood samples were immediately centrifuged and plasma was separated and stored in a deep freezer. All the plasma samples were analyzed in a single sitting using ELISA method, and computed results were obtained in μmol/l. Statistical analysis was done using GraphPad Instat statistical software.

Ethical clearance was obtained from Institutional Ethical Committee (IEC) and written informed consent was taken from all participants.

3. Results

The study cohort consisted of 50 participants (Table 1). Out of these, 30 (60%) were cases who had delivered babies with congenital heart defects and 20 (40%) were controls who had delivered normal babies. 28 participants (56%) were from rural background and 22 (44%) were from urban background. 17 (56.67%) of the cases were from rural background and 13 (43.3%) were from urban background. Out of the 20 controls, 11 (55%) were from rural background and 9 (45%) were from urban background.

The distribution of congenital heart defects in the babies is shown in Table 2.

The plasma homocysteine levels (tHcy) levels in cases and controls are shown in Table 3.

Out of 30 cases, 14 (46.6%) had a tHcy level more than 15 μmol/l and all these women had delivered babies who were found to have congenital heart diseases. Out of controls, only 3 (15%) had a tHcy level more than 15 μmol/l.

Out of 30 cases, 16 (53.33%) had a tHcy level less than 15 μmol/l and out of 20 controls, 17 (85%) had a tHcy level less than 15 μmol/l. These differences were statistically significant, with a p value of 0.02 and χ^2 of 5.362 (Table 4).

Among the 30 babies with congenital heart diseases, the maternal plasma tHcy levels were compared in various defects. In babies with ventricular septal defects, the maternal plasma tHcy level was in range of 5.5–46.88 μmol/l, with a mean level of 13.30 μmol/l. in babies with Tetralogy of Fallot, the maternal plasma tHcy level was in range of 17.5–46.88 μmol/l, with a mean level of 40.07 μmol/l. In babies with Transposition of Great Vessels, the maternal plasma tHcy level was in range of 29.28–46.83 μmol/l, with a mean level of 40.93 μmol/l in babies with Tricuspid atresia, the maternal plasma tHcy level was in range of 8.45–41.25 μmol/l, with a mean level of 24.89 μmol/l.

Table 1
Baseline characters of cases and controls.

Character	Cases	Controls
Median maternal age	32.2 years	32.6 years
Residential background	17 rural, 13 urban	11 rural, 9 urban
Mode of delivery	12 LSCS, 18 NVD	12 NVD, 8 LSCS
Mean maternal hemoglobin	11.1 g/dl	11 g/dl
Maternal cigarette/alcohol use	Nil	Nil

LSCS – lower segment caesarian section; NVD – normal vaginal delivery.

Table 2
Distribution of congenital heart defects in the babies.

Type of cardiac defect	Number of patients	Percentage
Ventricular septal defect	19	63.34
Tetralogy of Fallot	6	20
Transposition of Great Vessels	3	10
Tricuspid atresia	2	6.66
Total	30	100

Table 3
The plasma homocysteine levels (tHcy) levels in cases and controls.

	Range of plasma tHcy in μmol/l	Mean plasma tHcy in μmol/l	S.D.
Cases	5.5–46.88	24.36	16.6
Controls	7.66–45.6	14.16	13.14

$p = 0.013$.

Table 4
Risk of CHD in association with maternal plasma homocystiene levels.

	tHcy <15 μmol/l		tHcy >15 μmol/l	
	Number	Percent	Number	Percent
Cases	16	48.49	14	82.35
Controls	17	51.51	3	17.65
Total	33	100	17	100

$\chi^2 = 5.362$, $p = 0.02$.

4. Discussion

Congenital heart defects are the leading cause of deaths due to congenital anomalies.[9,10] Congenital heart defects have now surpassed anencephaly and spina bifida as a leading cause of infant deaths. Although the diagnostic and treatment modalities for congenital heart diseases have improved vastly, the goal of medical and public health personnel should be to find effective means for primary prevention of congenital heart defects.

In this study, ventricular septal defects were the most common congenital cardiac defects seen in the newborn babies. This is similar to the incidence of ventricular septal defects in the general population as reported by Goldmuntz.[11]

We observed that 46.67% of the study group subjects had a fasting hyper-homocysteinemia, as compared to only 15% in the control group. This difference was statistically significant ($p = 0.021$). Also, the mean fasting total plasma homocysteine levels in the study group were higher (24.36 μmol/l) than that in the control group (14.16 μmol/l). This difference was also statistically significant ($p = 0.013$). Livia et al.[5] also found similar results in their study. They found that mean fasting plasma homocysteine levels in 27 women who had given birth to babies with congenital heart diseases was higher than in those who gave birth to normal babies. They observed fasting hyper homocysteinemia in 46.2% of study group subjects as compared to 14.3% controls. They also carried out median methionine levels after loading plasma homocysteine and found that these concentrations were not higher in the study group.

In a recent study by Verkleij-Hagoort et al.,[12] it was seen that a high maternal fasting tHcy level was associated with a threefold higher risk of a child with congenital heart defect in a concentration dependant manner. Just like our results as depicted in Table 3, they saw that the risk for CHD increased with increasing maternal tHcy concentrations.

In another recent study by Charlotte et al.,[13] it was seen that just like our results, case subjects had higher mean concentrations of homocysteine ($p = 0.001$) than did control subjects.

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Our study further revealed that the mean total plasma homocysteine levels in mothers who delivered babies with Tetralogy of Fallot and Transposition of Great Vessels were higher (40.93 μmol/l and 40.17 μmol/l respectively). The mean total plasma homocysteine levels in mothers who delivered babies with ventricular septal defects and Tricuspid atresia were comparatively lower (13.3 μmol/l and 24.89 μmol/l respectively). This suggests a possibly stronger association of occurrence of Transposition of Great Vessels and Tetralogy of Fallot with maternal hyperhomocysteinemia.

Since the neural crest cells contribute to the outflow portion of the septum of heart,[14] it can be assumed that the altered homocysteine metabolism, as reported in neural tube defects, may play the same role in congenital heart defects. No increase in incidence of both these defects in newborns has been reported probably because these fetuses are aborted in early pregnancy.

In a number of studies,[15,16] the role of periconceptional multivitamins containing folic acid and the reduced risk of occurrence of congenital heart diseases in offsprings has been studied. Normalization of plasma homocysteine levels has been cited as one of the possible mechanisms of folic acid in these cases.[6]

Thus, we conclude from this study in Asian population that increased levels of maternal serum homocysteine are associated with increased risk of occurrence of congenital heart defects in their offsprings, suggesting that maternal hyperhomocysteinemia is an independent risk factor for congenital heart defects. It would be prudent to recommend folic acid supplementation in women before and during early pregnancy to help prevent congenital heart defects in babies, just as has been recommended by Centre for Disease Control (CDC) for preventing neural tube defects.[17,18] In 1996, the United States Food and Drug Administration (FDA) mandated that by January 1, 1998 all grain products labeled as 'enriched', such as breads and cereals, have folic acid added to them to help reduce the risk of neural tube defects. Similar legislation is needed in our Asian countries.

5. Conclusions

Thus, we conclude from this study in Asian population that increased levels of maternal serum homocysteine are associated with increased risk of occurrence of congenital heart defects in their offsprings, suggesting that maternal hyperhomocysteinemia is an independent risk factor for congenital heart defects. It would be prudent to recommend Folic acid supplementation in women before and during early pregnancy to help prevent congenital heart defects in babies, just as has been recommended by Centre for Disease Control (CDC) for preventing neural tube defects.

Conflicts of interest

The authors have none to declare.

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